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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,162	09/22/2003	Ronald R. Breaker	25006.0016U2	4368

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/669,162	**Applicant(s)** BREAKER ET AL.	
	Examiner Jane Zara	**Art Unit** 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 14 January 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 13 November 2007. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: _____.

   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☒ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Please see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Attachment

The amendments have not been entered because they require consideration of new limitations. The IDS has not been considered because there is no reason that this information had not been submitted earlier in prosecution (before final rejection).

Claims 1-7, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office actions mailed 12-12-06 and 7-10-07.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of searching for candidates of the genus comprising RNA comprising any riboswitch operably linked to a coding region, which riboswitch regulates expression of the RNA, and which riboswitch and coding region are heterologous to each other, and which riboswitch comprises an aptamer domain, a control strand and an expression platform domain comprising a regulated strand, and which regulated and/or control strands form a stem structure, and which riboswitch is optionally derived from a naturally occurring guanine-responsive riboswitch, and which riboswitch is activated by a trigger molecule and produces a signal upon activation by the trigger molecule, does not reasonably provide enablement for predictably making and designing the members of the broad genus of molecules

claimed without undue experimentation for the reasons of record set forth in the Office action mailed 12-12-06 and 7-10-07.

Applicant's arguments filed 1-14-08 have been fully considered but they are not persuasive. Applicant argues that no undue experimentation is required for the full scope claimed and that adequate written description has been provided for the broad genus of nucleic acid molecules claimed because the generic primary and secondary structural features of riboswitches described in the specification reproduce the necessary three dimensional structures without the need of guidance or further description, that consensus elements of other guanine aptamers have been identified, and that aptamers in general are well known in the art and can be produced by known techniques and are useful with the riboswitches disclosed in the specification. Applicants also argue that that post filing publications describe the crystal structures of riboswitches and therefore the conserved and consensus structural elements that were identified in the present application have been found to be significant in determining the crystal structures of the riboswitches.

Contrary to Applicant's assertions, in order to satisfy written description and enablement requirements for the broad genus of compounds claimed, Applicants must have been in possession of a representative number of species at the time of filing. The post filing publications do not substitute for this requirement at the time of filing. The specification teaches alignment of sequences which are known to serve as binding sites for several ligands known to be recognized by natural riboswitches, and putative riboswitches based on these alignments, as well as proposed models for secondary

structures and putative pseudoknot structures (pp. 20-23). The specification also teaches the structural probing of various putative riboswitches e.g. figure 16), and possible mechanisms of riboswitch control (e.g. figure 17).

The specification also teaches the 5'-UTR of the *B. subtilis* xpt-pbuX mRNA as a potential guanine-specific riboswitch (figures 24-26 of the instant specification). In addition, the specification teaches a comparison between this 5'-UTR fragment (of 185 nucleotides) and other bacterial sequences, whereby a purportedly conserved RNA motif, termed a "G box" has been identified as domain for a guanine-riboswitch, suggesting that conserved secondary and tertiary structures are likely a pre-requisite for adopting the required conformation for riboswitch function. But the three-dimensional fold necessary for riboswitch function was not unambiguously identified at the time of filing (see e.g. p. 139 of the instant specification). These purported structures and mechanisms do not satisfy the written description requirements for the broad genus of compounds claimed. Concise features, not purported structures, which describe the required conformations and detailed molecular structures characterizing the broad genus of compounds claimed are missing from the art and from the disclosure at the time of filing.

The specification teaches the identification of a 5'-UTR fragment of the *B. subtilis* xpt-pbuX mRNA as a potential guanine-specific riboswitch (figures 24-26 of the instant specification), as well as teaching a comparison between this 5'-UTR fragment (of 185 nucleotides) and other bacterial sequences, whereby a purportedly conserved RNA motif, termed a "G box" has been identified as a domain for a guanine-riboswitch,

suggesting that conserved secondary and tertiary structures are likely a pre-requisite for adopting the required three-dimensional fold necessary for riboswitch function (see e.g. p. 139 of the instant specification). The ability to test various sequences for their ability to cleave target nucleic acid strands in the presence of various ligands, and the postulation of required, yet undefined structural constraints for riboswitch activities is not representative of the ability to predictably make and use the broad genus of compounds claimed.

For these reasons the instant rejections are maintained.

Claims 1-7 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Breaker (Curr. Opin. Biotech., 13: 31-39, Feb. 1, 2002) for the reasons of record set forth in the Office actions mailed 12-12-06 and 7-10-07.

Applicant's arguments filed 1-14-08 have been fully considered but they are not persuasive. Applicant argues that the teachings of Breaker do not properly anticipate the instant invention because Breaker does not disclose the elements of the claimed riboswitch molecule, but instead discloses a ribozyme. Applicant argues that Breaker does not disclose linkage of a riboswitch to a coding region and regulation of RNA expression by a riboswitch.

Contrary to Applicant's assertions, Breaker properly anticipates the instant invention. Breaker, for instance teaches nucleic acid constructs containing biosensor elements recognized by RNA molecular switches (see second full paragraph on p. 31 of Breaker). Breaker teaches a regulatable gene expression construct, comprising RNA

comprising a riboswitch (e.g. regulatable by effector molecules such as ATP) and a coding region (e.g. a ribozyme which, when triggered allosterically, cleaves, and hence inhibits expression, a target RNA sequence). See also first full paragraph on p. 32, describing RNA molecules that respond allosterically to chemical signals such as ATP. Breaker teaches gene expression constructs comprising the elements claimed, e.g. a riboswitch, derived from either a naturally occurring or a non-naturally occurring riboswitch, operably linked to a coding region, which riboswitch comprises an aptamer domain and an expression platform domain, which aptamer domain comprises a P1 stem, which P1 stem comprises an aptamer strand and a heterologous control strand, and the expression platform comprises a regulated strand, and which regulated or control strand forms a stem structure, and which riboswitch produces a signal when activated by a guanine trigger molecule (see the text on p. 31; fig. 2 on p. 33; fig. 3 on p. 34; text on p. 38).

Furthermore, the coding region, which is linked to the riboswitch, is optionally self-cleaving, thereby satisfying the limitation of regulating RNA expression of the coding region by a riboswitch (see page 38 of Breaker: Effector-induction of a self-splicing ribozyme could be used to process mRNA precursors to produce expression-competent messages in response to the presence or absence of analyte. Similarly, self-cleaving ribozymes could be created that permit the analyte-induced destruction or stabilization of mRNAs."

The instant rejection is hereby maintained for the reasons set forth above.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
2-5-08

JANE ZARA, PH.D.
PRIMARY EXAMINER